Oscillatory patterns in the electroencephalogram at sleep onset

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DOI: https://doi.org/10.1093/sleep/zsz096

Oscillatory EEG patterns at sleep onset

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Published in Sleep: doi: 10.1093/sleep/zsz096

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Abstract

Falling asleep is a gradually unfolding process. We investigated the role of various oscillatory activities including sleep spindles and alpha and delta oscillations at sleep onset (SO) by automatically detecting oscillatory events. We used two datasets of healthy young males, eight with four baseline recordings, and eight with a baseline and recovery sleep after 40 h of sustained wakefulness. We analyzed the 2-min interval prior to SO (stage 2) and the five consecutive 2-min intervals after SO.

The incidence of delta/theta events reached its maximum in the first 2-min episode after SO, while the frequency of them was continuously decreasing from stage 1 onwards, continuing over SO and further into deeper sleep. Interestingly, this decrease of the frequencies of the oscillations were not affected by increased sleep pressure, in contrast to the incidence which increased. We observed an increasing number of alpha events after SO, predominantly frontally, with their prevalence varying strongly across individuals. Sleep spindles started to occur after SO, with first an increasing then a decreasing incidence and a continuous decrease in their frequency. Again, the frequency of the spindles was not altered after sleep deprivation. Oscillatory events revealed derivation dependent aspects. However, these regional aspects were not specific of the process of SO but rather reflect a general sleep related phenomenon. No individual traits of SO features (incidence and frequency of oscillations) and their dynamics were observed. Delta/theta events are important features for the analysis of sleep onset in addition to slow waves.

Key words: Alpha activity; delta activity, theta activity; sleep spindles; transition to sleep; trait

Statement of Significance

Oscillatory events in the EEG may help to get a better understanding of the sleep onset process. Alpha events disappeared, and delta/theta events emerged at the transition from wake to sleep stage 1 and sleep spindles were detected after the transition from stage 1 to stage 2. The dynamics of the frequency of events was not affected by increased sleep pressure. Interestingly, no trait-like aspects of sleep onset features (incidence and frequency of oscillations) and their dynamics were observed. The analyses revealed that delta/theta events are important features of the sleep onset process in addition to slow waves.

Introduction

Sleep onset (SO) has been operationally defined in various ways, often as the first epoch other than wakefulness [1-3]. In most subjects this usually is the first epoch of stage 1 (N1) defined as the disappearance of alpha activity in the EEG (if present) and the emergence of low amplitude, mixed frequency activity for more than 50 % of the epoch [2]. In particular, occipital EEG derivations may be useful to "visualize alpha rhythm and its disintegration at sleep onset" [1]. Furthermore, slow eye movements may help to identify SO [1]. According to Rechtschaffen and Kales [3] SO was defined the first three consecutive epochs of stage 1 (or any other deeper stage of sleep). On the other hand, the American Academy of Sleep Medicine (AASM) defines the moment of SO as the first appearance of any 30-s epoch containing at least 15 s (50 %) of any sleep stage sleep [2].

Classical sleep stage scoring captures the macro structure of sleep. However, this is partially a subjective measure relying on human visual pattern recognition. Furthermore, the discrete stages do not reflect the gradual changes that occur during sleep. They are not suited to describe the process of falling asleep, because they do not reveal the micro structure [4]. This limitation was noticed early on by Kleitman: "Whereas it is easy to distinguish between the conditions of alertness, or being wide awake, and definite sleep, the passage from one to the other involves a succession of intermediate states, part wakefulness and part sleep in varying proportions - what is designated in Italian as dormiveglia, sleep-waking" ([5], p. 71). Thus, Hori et al. [6] proposed a nine-stage SO scoring system based on 5-s epochs to trace more accurately the W-S transition (H1: wakefulness … H9: stage 2 sleep, i.e. epoch with at least one clear spindle).

We were interested to see whether there are just two distinct states 'wake' and 'sleep' or whether there is a transitional stage and investigated the role of various oscillatory activities including sleep spindles and alpha and delta oscillations at SO. Even when the process of SO is a gradual phenomenon unfolding continuously over time [7-9], data have to be aligned for statistical comparisons. As there is no "right" definition of the moment of SO, we pragmatically considered the first occurrence of stage 2 (indicating unequivocal signs of sleep) as SO, as suggested by and applied

in many other studies [10-16] in order to align the data. We implemented quantitative EEG analysis (detection of oscillatory events) to track the wake-sleep transition and addressed how increased sleep pressure (sleep deprivation) affect the process of SO. Sleep EEG power in humans has been shown to be trait-like, i.e. within-subject variability was smaller than between subject variability [17-23]. Thus, we investigated whether oscillatory patterns at SO also have trait-like features.

Methods

Data

The analyses were performed on existing datasets of healthy young male participants of baseline recordings of a previous study (***SRD***) investigating the effect of selective REM sleep deprivation [24] and of a study investigating the effects of sleep deprivation (***MAP***) on EEG topography [25].

Eight healthy, right-handed men (24.1 ± 0.6 years; mean ± SEM) participated in the SRD study, which consisted of two sessions of nine consecutive nights: adaptation night followed by two baseline nights (time in bed 23:00 to 7:00 hours) and six experimental nights. The two sessions were 28 days apart, except in one participant with only 23 days between the sessions [24].

Eight healthy, right-handed men (23.0 ± 0.46 years) participated in the MAP study, consisting of an adaptation night, a subsequent baseline night (23:00 to 7:00 hours) and a recovery night (23:00 to 11:00 hours) after 40 h of sustained wakefulness.

The local ethical committee for research on human subjects approved both study protocols, and written informed consent was obtained from the subjects prior to the study.

The EEG derivations F3A2, C3A2 and O1A2 were analyzed (sampling rate 128 Hz; band-pass filter 0.16-49 Hz (SRD); 0.16-30 Hz (MAP)). Sleep stages were visually scored according to standard criteria ([3]; derivation C3A2).

Sleep onset

As mentioned in the introduction, for statistical analyses of the temporal evolution of brain activity at SO, data of different participants must be aligned. Thus, in our case SO was operationalized as the first occurrence of an epoch of stage 2. We analyzed the 2-min interval prior to SO and the five consecutive 2-min intervals after SO. We were restricted to the 2-min prior to SO as this was the common interval available in all participants and conditions. With our alignment of the data, we basically compared stage 1 (2 min prior to SO) with stage 2 (SRD and baseline of MAP) and with stage 2 followed by SWS (recovery of MAP). Oscillatory events in the 2-min intervals were treated stage independent. Thus, occasionally episodes of wakefulness were included after SO. However, hardly any oscillatory events were detected in these epochs (see individual data provided in the supplement).

Latencies to stage 1 and 2 were measured from lights out.

Detection and analysis of oscillatory events

Oscillatory events in the sleep EEG (derivations F3A2, C3A2, and O1A2) were detected with a previously published algorithm [26-28]. An autoregressive model of order 8 was fit to overlapping 1-s segments of the EEG with a time step of one sampling interval (1/128 s; [28]). Thus, a maximum of four stochastically driven harmonic oscillators, with damping and frequency varying in time, could be identified. Whenever the damping at one or more frequencies was smaller than a predefined threshold, an oscillatory event was detected [26]. One-second segments of distinct events overlapping in time and frequency were merged into a single event [28]. For details see [4,26-28]. Events were characterized by their time of occurrence (lowest damping), mean frequency and duration. We analyzed the event ratio, i.e. the ratio between the sum of the durations of the events in a specific frequency band divided by the total time in a particular window. The event ratio, combining the duration and the rate of events is a robust measure of oscillatory activity [27].

To investigate the temporal evolution, we examined three specific frequency bands: delta/theta (1.5 -7.0 Hz), alpha (8.0-12.0 Hz) and sigma (12.0-16.0 Hz) in 2-min intervals (episodes 1 to 6), 2-min prior to SO and five consecutive intervals after SO. The bands were determined based on visual assessment of the occurrence of oscillatory events, the histograms of the event ratios, and power density spectra in each subject (Figure 1). We did not distinguish between (fast) delta and theta oscillations because the oscillatory events that occur at the beginning of the transition period have frequencies between 3 and 5 Hz and thus would be classified in part as theta oscillations by using the usual frequency band definitions. However, we think that such a distinction would be purely artificial, because these events occur in single band and seem to exhibit similar properties (Figure 1 and Figures S1 and S2). Additionally, we investigated the average frequency of the events in those bands (average weighted by the duration of the events). Slow delta events (< 1.5 Hz) were excluded, because the employed method is not optimal for detecting and characterizing them (see discussion). Derivations F3A2, C3A2, and O1A2 were analyzed. To enhance readability, we refer to the derivations as F3, C3, and O1.

Statistical analyses

All statistical analyses were carried out with the statistical computing language and environment R (version 3.4.4, 2018-03-15). For our analyses we used linear mixed models, as implemented in the 'lme4' package ([29], version 1.1.17).

For the analysis of SRD data, we chose derivation (F3, C3, O1), episode (1 to 6) and its interaction terms as fixed effects. Night was not a fixed effect because the four nights were the repeated measures within subjects. Random effects (intercepts) were applied for subject, and in a nested fashion for night, episode, and derivation per subject (see Supplemental Material).

For the MAP data we additionally included night (baseline, recovery) as a fixed factor, again with all possible interaction terms. Therefore, night was excluded from the random effects.

For each frequency band (delta/theta, alpha, sigma) and dataset (SRD and MAP) we analyzed the event ratio and mean frequency as response. The event ratio has a value between [0,1) and had to be transformed into an unbounded value $(-\infty, +\infty)$ because of the linearity of the mixed model. Zero values were randomly replaced by a value from a uniform distribution in the interval (0, 1/120 s) and a Fisher-z transformation was applied. More information can be found in Supplemental Material. Mean frequency did not need to be transformed.

The normality assumptions of the linear mixed models were examined by means of Tukey-Ascombe and Normal Q-Q Plots of the residuals (also faceted by subjects and by other factors). Global ANOVA F-tests were used to see if each fixed effect had an overall effect. Post-Hoc tests included in the package 'emmeans' of R were used to test hypothesis driven assumptions. All tests of interest were adjusted per fitted model for multiple testing by the Benjamini and Hochberg False Discovery Rate (FDR) control procedure [30]. Significant effects were assessed by looking first at the corresponding factor (e.g. topography factor 'derivation') followed by a post-hoc test ($p<0.05$, FDR corrected). Significances are reported in Tables 1 and 2.

Intraclass correlation coefficients (ICCs) were determined as the between-subject variance divided by the between- plus within-subject variances [31] with the variances estimated with the mixed models. ICCs could be determined for the SRD data with four recordings per participant.

Results

Average latency to stage 1 in the SRD data was 5.9 ± 1.3 (SEM) and to stage 2 (sleep onset) 8.7 ± 1.5 min. In the baseline of the MAP data, latency to stage 1 was 7.1 ± 1.6 and to stage 2 12.0 ± 1.6 min and both were shorter (stage 1 by 4.8 ± 1.3; stage 2 by 7.8 ± 1.3 min; $p<0.005$, paired t-test) after sleep deprivation (latencies at recovery: stage 1, 2.3 ± 0.7; stage 2, 4.2 ± 1.2 min). To assess trait aspects, i.e. to measure intra-individual stability and interindividual variability, we determined the

ICCs of the two latencies for the SRD data with four recordings (stage 1: ICC = 0.36; stage 2: ICC = 0.34). These low values indicate that there is no trait-aspect in the latencies to stage 1 and 2.

We investigated the occurrence of oscillatory events during the process of falling asleep (Figure 1, derivation C3; for frontal and occipital derivations see Figures S1 and S2). The events clearly segregated into the three bands delta/theta, alpha, and sigma (spindles). Alpha and sigma events resulted in a corresponding peak in the power density spectra. These activities were also visible in the spectrograms. At an individual level, delta/theta and alpha events generally did not overlap, neither temporally nor spatially (Figures S3 to S8) as it is suggested by the pooled events. Alpha events (8-10 Hz) were present throughout waking and disappeared with the onset of stage 1 (in all derivations; Figures S3 to S5). Delta/theta events (1.5-7 Hz) started to occur in stage 1 and continued into sleep. Their frequency was decreasing with increasing time (see below for statistical analyses). Sleep spindles appeared with the onset of stage 2 and with the deepening of sleep, their frequency decreased (F3, C3). Shortly after SO alpha events started to emerge (all 3 derivations).

Alpha events during waking predominated occipitally (O1; Figure S3) and frontally after SO (F3; Figure S1), while delta/theta events prevailed centrally (C3; Figure 1). For statistics on topographical aspects see below.

For statistical analyses of the temporal evolution and topography, oscillatory events (event ratio, mean frequency of the events) were analyzed in six 2-min episodes (1 to 6; 2 min prior to SO, five consecutive 2-min intervals after SO). We restricted the analysis to two min prior to SO (episode 1) as this was the only episode prior to SO where all participants contributed across the studies and conditions. In the next sections we summarize the main significant changes/differences in Figures 2 to 4 based on the post-hoc tests (FDR corrected). The corresponding p-values are provided in Tables 1 and 2, with blue colors indicating a decrease or lower values (with increasing time or from anterior to posterior derivations) and red colors increases or higher values. If appropriate, overall effects of the mixed model are reported in the text.

Delta/theta events (Figure 2)

Event ratio

Delta/theta events started to occur already in stage 1 (Figures 1, S1 and S2). Thus, the event ratio after SO (episode 2) was similar to the one before SO (episode 1; Table 1). However, in recovery (MAP) the event ratio at C3 and O1 increased from episode 1 to 2. Delta/theta events decreased with time after SO (from episode 2 to 6; Table 1) at F3 and C3 in the SRD data whereas the MAP data did not show this temporal evolution. In both datasets highest event ratios were observed at the central derivation (C3>F3>O1; Table 2). Increased sleep pressure resulted in an elevated event ratio after SO (overall factor 'condition', $p<0.00001$). Again, to assess trait aspects, we determined the ICC of the temporal evolution of the event ratio in the SRD data (overall, taking topography and time into account; ICC = 0.16).

Frequency

The mean frequency of delta/theta events was decreasing with time (overall linear trend) by approximately 0.6 Hz (SRD; in F3 and C3 decrease from episode 1 to 6; Table 1). In SRD, a topographic antero-posterior gradient was observed with the highest frequency at the occipital derivation (F3<C3<O1; Table 2). In the MAP study, the highest frequency was also at the occipital derivation, but F3 and C3 did not differ. Increased sleep pressure did not affect the frequency of the events (overall factor 'condition', $p>0.1$; Figure 2, lower right panels). The ICC of the SO process was 0.01 (overall).

Alpha events (Figure 3)

Event ratio

Alpha events were present during waking and by definition a dropout of alpha occurred at the transition to stage 1 (Figures 1, S1 to S8). Alpha activity was strongest occipitally (Figures 1, S1 and S2). After SO, the event ratio increased as a function of time (episode 2 to 6) in F3 and C3 (SRD data;

Table 1). The strongest increase occurred in F3 (Table 2). In both studies, highest event ratios were observed at frontal/central derivations (SRD: F3>C3≈O1; MAP: F3≈C3>O1; Table 2). Increased sleep pressure resulted in an elevated event ratio after SO (overall factor 'condition', $p<0.001$) and an increase as a function of time was present at F3 (episode 2 to 6; Table 1).

Large interindividual differences were present with some participants showing high alpha activity (SRD: 5, 8, 15; MAP: 11, 16) and the ICC of the transition process was 0.31.

Frequency

In the SRD data the mean alpha frequency increased at the SO transition (episode 1 vs 2; Table 1) and decreased occipitally with increasing time into sleep (Table 1). A similar decrease in the MAP data did not reach significance. Sleep deprivation did not affect the frequency of the alpha events (overall factor 'condition', $p>0.1$; Figure 3, lower right panels). The ICC the SO process was 0.20.

Sigma events (Figure 4)

Event ratio

Sigma events occurred after SO and showed first an increase (SRD: episode 1 to 4; MAP: 1 to 2) and then levelled off (plateau; Table 1). With increased sleep pressure, the plateau was reached earlier (Table 1). Additionally, sleep deprivation resulted in an overall lower level of the event ratio (factor 'condition', $p<0.0002$). The highest event ratios were observed at the central derivation in both studies (O1<F3<C3; Table 2). The ICC the SO process was 0.22.

Frequency

The mean frequency of sigma events (fast spindles) decreased with time after SO (episode 2 to 6; Table 1) in all three derivations of the SRD data. In the MAP data a similar picture emerged, however only at C3 in recovery was a significant decline observed. A topographic antero-posterior gradient was present with the lowest frequency at the frontal derivation (SRD: F3≈C3<O1; MAP: F3<C3<O1;

Table 2). Increased sleep pressure did not affect the frequency of the sigma events (overall factor 'condition', p>0. 1; Figure 4, lower right panels). The ICC of the transition process was 0.33.

Discussion

Classically the process of falling asleep was described as a sequence of states with each of these states accompanied by specific dynamic patterns in the EEG: The stop of the occipital alpha oscillations marks the transition from the awake state to sleep stage 1, which was related to a diffuse delta/theta activity and the occurrence of vertex waves, large amplitude half waves corresponding to frequencies of 2-3 Hz at a later stage [32,33]. The transition to sleep is completed with the first occurrence of a K-complex or sleep spindles, the marker of sleep stage 2 [12,13,15,34]. The older literature made sometimes finer distinctions within sleep stage 1: light drowsiness vs deep drowsiness, with the latter connected to the occurrence of vertex waves [35].

More recently it was proposed to consider the EEG patterns in the slow wave frequency range such as vertex waves, K complexes or slow waves in deep sleep, as expression of the very same phenomenon: the so called slow oscillation [9]. They postulated that the temporal evolution of slow oscillations at the SO transition resulted from two distinct synchronization processes, first dominated by "Type I" slow waves (mediated by subcortical arousal promoting structures in the pons), followed by "Type II" slow waves (originating from cortico-cortical synchronization processes). Only "Type II" slow waves showed a homeostatic behavior across the night [36]. The slow waves of Siclari et al. [9,36] concerned frequencies in the range of 0.5-2 Hz whereas we analyzed activity in the 1.5-7 Hz range, clearly a different type of oscillations. As we pointed out previously, it might be meaningful to separately analyze slow and fast delta activity [19,27] as their homeostatic behavior was different. Furthermore, we observed in pre-school children that the slowing of fast delta events and the disappearance of alpha events most clearly indicated the transition into sleep [28]. Also, the current results support this notion. Fast delta oscillations probably have two different generating

components, a cortical and/or a thalamic one [37]. Taken together, these findings suggest a specific functional role of fast delta oscillations that warrants further investigation.

Based on our analysis we cannot make any decisive statements about the neurophysiological origins of the observed patterns. But we provide a systematic description of the oscillatory patters on the phenomenological level that is not affected by the subjective component of the human pattern recognition present in the older literature.

In our analysis of the oscillatory events the wake-sleep transition appears as a combination of discrete qualitative and more continuous quantitative changes. The qualitative changes were, as expected, directly connected to state transitions:

1. The disappearance of alpha events (alpha dropout) and the occurrence of delta/theta events was related to the transition from the awake state to sleep stage 1.
2. The detection of a significant number of oscillatory events in the spindle frequency range started after the transition from stage 1 to stage 2.

The more continuous, quantitative changes were more interesting:

1. Delta/theta events: The event ratio reached its maximum in the first 2-min episode after sleep onset (episode 2 in Fig. 2), while the event frequency was continuously decreasing from stage 1 onwards, continuing over sleep onset and further into stage 2 (Figs. 1, S1 and S2). The latter pattern was the main reason for not making a distinction between theta and delta events. Interestingly, this decrease of event frequency was not affected by increased sleep pressure, in contrast to the event ratio which increased significantly. In contrast, slow-wave activity (power in 0.75-4.5 Hz range; [38]) and slow waves [9] showed a gradual buildup in this time window.
2. We observed an increasing number of alpha events after SO, predominantly frontally, with their prevalence varying strongly across individuals, which was already observed in previous analyses of the same data [26,27].

   The relevance and interpretation of the decreasing event frequency of occipital alpha oscillations is somehow unclear, because we observed only a small number of events and it is

not clear whether they are related to awake alpha, NREM sleep alpha [39] or slow spindles (less probable at occipital derivations). However, also here the dynamics was not affected by sleep deprivation.

3. Sleep spindles showed the expected pattern: starting to occur after SO, with first an increasing then a decreasing event ratio and decreasing in their event frequency (compare [26] for a decrease with deepening of sleep). Again, the event frequency did not decrease faster after sleep deprivation. This contrasts with the finding of [27], where on average over the whole night spindle frequencies were decreased with increased sleep pressure.

These observed discrete qualitative and continuous quantitative changes do not provide any indication that a finer differentiation into short discrete stages of the SO process would be needed.

The 2-min episode after SO (episode 2) seems to be special in the way that the event ratio of delta/theta events was maximal and the spindle (and occipital alpha) frequency was maximal. This resembles a finding from Olbrich and Achermann [26], where we observed that the event density of delta events and the frequency of spindles was higher in stage 2 occurring within REM sleep episodes compared to stage 2 occurring within NREM sleep episodes. Visual inspection of the event patterns over the entire night ([27] supplement) indicates that this pattern seems to occur also at transitions between NREM and REM sleep suggesting that the brain at sleep onset might be in a similar state as at the transitions between NREM and REM sleep. Also Bodisz et al. [40] described stage 1 before SO as 'REM sleep like'.

The overall dynamics of the wake-sleep transition, in particular the frequency of the oscillations, was only partially affected by sleep deprivation. If one considers the sleep latency, the average duration of stage 1 sleep or the time until the first deep sleep it appears as if the wake-sleep transition was faster after sleep deprivation, i.e. a higher sleep pressure accelerates the transition dynamics. However, the dynamics of event frequencies for delta/theta, alpha and spindle events seemed not to be affected by sleep pressure. This finding indicates that more than one mechanism is controlling the state dynamics during sleep onset.

Individual traits

We found large inter-individual differences both for the event ratios and the event frequencies for all types of events. For the data analyzed in this paper they are described in Olbrich and Achermann [26] (SRD) and in Olbrich et al. [27] (MAP). Corresponding individual traits were also described for spectral features [18-21,41]. However, we did not find any trait like effects specific for the wake-sleep transition and its dynamics: both latencies to stage 1 and stage 2 sleep did not show trait like aspects in contrast to adolescents, where sleep latency was genetically determined [42] as well as transition patterns (dynamics of event ratios and event frequencies) in the different frequency band (ICCs ≤ 0.36). Lowest ICCs were observed for delta/theta activity. According to published benchmark ranges [43] only ICC estimates > 0.61 are interpreted as 'substantial' or 'almost perfect'.

Topography

We observed EEG derivation specific differences compatible with the observations that the process of falling asleep is neither spatially nor temporally a uniform process [8,34,44]. In particular we observed temporal asynchronicity of the alpha dropout – usually it occurred later occipitally compared to frontal and central derivations and thus occipital alpha events were still observed in sleep stage 1, because sleep stages were scored in C3 according to Rechtschaffen and Kales [3]. In a few subjects (MAP 07, SRD 15) we even observed frontal delta/theta events while the occipital alpha activity was still present.

However, with 3 derivations a more detailed topographical analysis was not possible.

Interestingly, delta/theta events showed the highest incidence centrally and might reflect vertex waves and the strongest effect of sleep deprivation also occurred centrally. Thus, this is an indication that these events might be functionally different from slow waves or slow-wave activity with a frontal predominance [25,45]. Such events at the transition to sleep were also observed in preschool children (C3A2; [28]). We did not observe the occipital increase of theta activity after SO reported by Marzano et al. [13].

Alpha activity was strongest occipitally during waking and shifted towards frontal areas at the SO transition. F3 showed the strongest increase with time after SO and the strongest response to sleep deprivation.

As observed previously [13,25], fast sleep spindles revealed topographic aspects with the highest event ratios observed at the central derivation.

In summary, all types of oscillatory events revealed brain region dependent aspects. However, these regional aspects were not specific of the SO process but rather reflect a general sleep related phenomenon.

Methodological aspects

Our event analysis allows the characterization of specific temporally localized oscillatory activity independent of background activity. Thus, it is well suited to track the temporal evolution of the SO process. We employed an algorithm that does not rely on predefined frequency bands. Instead, we established the frequency bands based on the distribution of the detected events.

Also, Marzano et al. [13] identified oscillatory activity at the SO transition based on the better oscillation method capable of differentiating between oscillatory activity and background activity. Their proportion of time with significant oscillations is comparable to our event ratio resulting in similar findings. However, their detected oscillatory activity was broad band which did not reveal the distinct trends in the event frequencies we observed.

We analyzed the 2-min interval prior to SO (stage 2) and the five consecutive 2-min intervals after SO. Therefore, our results did not specifically track the occurrence of occasional wake episodes, arousals or stage shifts. Thus, the 2 min prior to SO consisted mainly of stage 1, and the 5 2-min intervals after SO of stage 2 (SRD and baseline of MAP) and of stage 2 followed by SWS (recovery of MAP). Nevertheless, we think that we adequately captured the global temporal evolution with our approach. For details we refer to the individual data provided in Figures S3 to S8.

Limitations

Several limitations need to be discussed. First, we investigated two small homogeneous samples of healthy young males who were good sleepers [24,45], which limits generalization of our findings. However, we observed similar oscillatory patterns at SO in a longitudinal study of preschool children [28]. Second, some of the changes observed in the SRD dataset were not reflected in the baseline of the MAP data. However, this is no contradiction as statistical power was better in the SRD (4 nights per participant) than MAP data (1 night per participant). Third, a detailed topographical analysis was not possible as our analyses were based on three referential derivations in the left hemisphere. Finally, slow delta events (< 1.5 Hz) had to excluded as the applied method to detect oscillatory activity is not well suited to identify and characterize slow oscillations with frequencies around 1 Hz and below due to the use of 1-s segments (see also [26,27] for further discussion).

Future directions

The current results and previous findings in the context of developmental aspects [28] suggest that "fast" delta oscillations (>2 Hz; delta/theta) may serve a specific functional role that warrants further investigation. Physiologically, this activity may have different generating components originating in the cortex and/or in the thalamus [37]. Delta/theta events were also observed in REM sleep and at the NREM-REM sleep transition (see supplementary data in [27,28]) again pointing to (a) specific functional role(s). Furthermore, future investigations should include a more detailed topography, other age groups and different sexes.

Conclusions

Our main and novel findings were: 1) The dynamics the frequency of events was not affected by increased sleep pressure. 2) No individual traits of sleep onset features and its dynamics were observed. 3) Delta/theta events are important features for the analysis of sleep onset in addition to slow oscillations.

Acknowledgement

The study was supported by the Swiss National Science Foundation grants 32003B_146643 and 320030_163439).

Disclosure Statement

Financial Disclosure: none.

Non-financial Disclosure: none.

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Figures

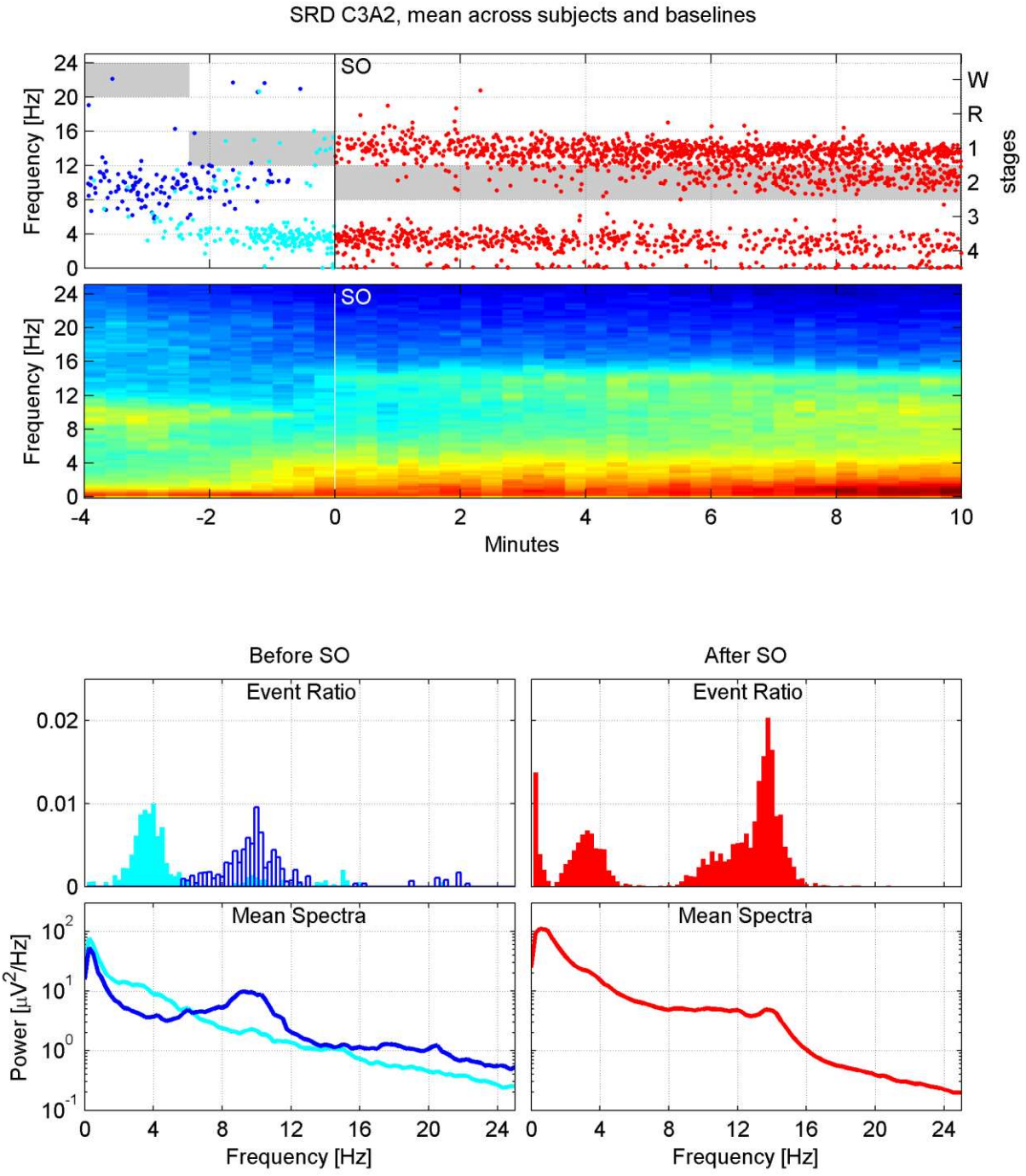

Figure 1: ***Top:*** Oscillatory events and spectrograms (derivation C3A2) at the transition into sleep, 4 min prior to and 10 min after sleep onset. Sleep onset was defined as the first occurrence of stage 2. Top panels: Occurrence of oscillatory events (frequency axis on left) pooled across the four baseline nights and the eight participants superimposed on average sleep stages (axis on right; W: waking, R:

REM sleep, 1-4: NREM sleep stages 1-4). “Averaging“ of stages was performed by first determining whether at least half of the recordings showed wake. If yes, wake was assigned as the average stage. If the majority of them revealed NREM sleep, the rounded average of the NREM sleep stages (values 1 to 4) was assigned as the average stage. Bottom panel: Average spectrogram (4 nights, 8 participants). Spectra were color coded on a logarithmic scale 0 dB = 1 $\mu V^2/Hz$; -10 dB  25 dB. ***Bottom:*** Average event ratios and power density spectra before and after sleep onset. Dark blue: waking; light blue: stage 1 (prior to sleep onset); red: stage 2 (after sleep onset). For derivations F3A2 and O1A2 see Supplementary Figures S1 and S2.

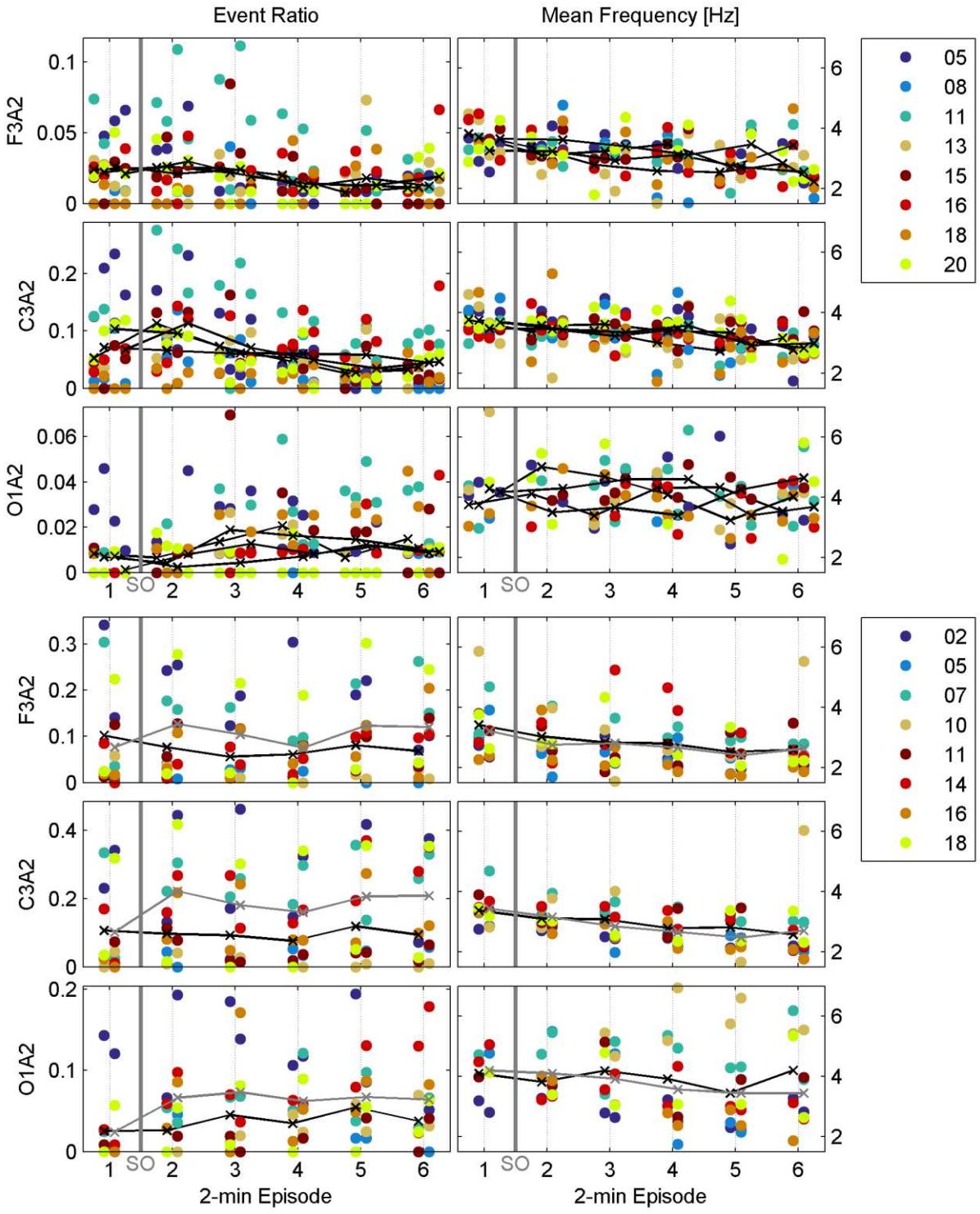

Figure 2: Temporal evolution of oscillatory events in the delta/theta (1.5 -7.0 Hz) band in 2-min intervals (episodes 1 to 6), 2-min prior to SO (episode 1) and five consecutive intervals after SO (episodes 2 to 6). Solid lines connect averages over subjects. Top three rows, events in frontal, central, and occipital derivations of the SRD data (4 baseline nights per participants). Bottom three rows, oscillatory events of the MAP data (baseline black and recovery grey after 40 h of sustained

wakefulness). Fist column: event ratio; second column: mean frequency of events. The numbers in the right boxes indicate the individual participants. Different subjects participated in the two studies (matching numbers are a coincidence).

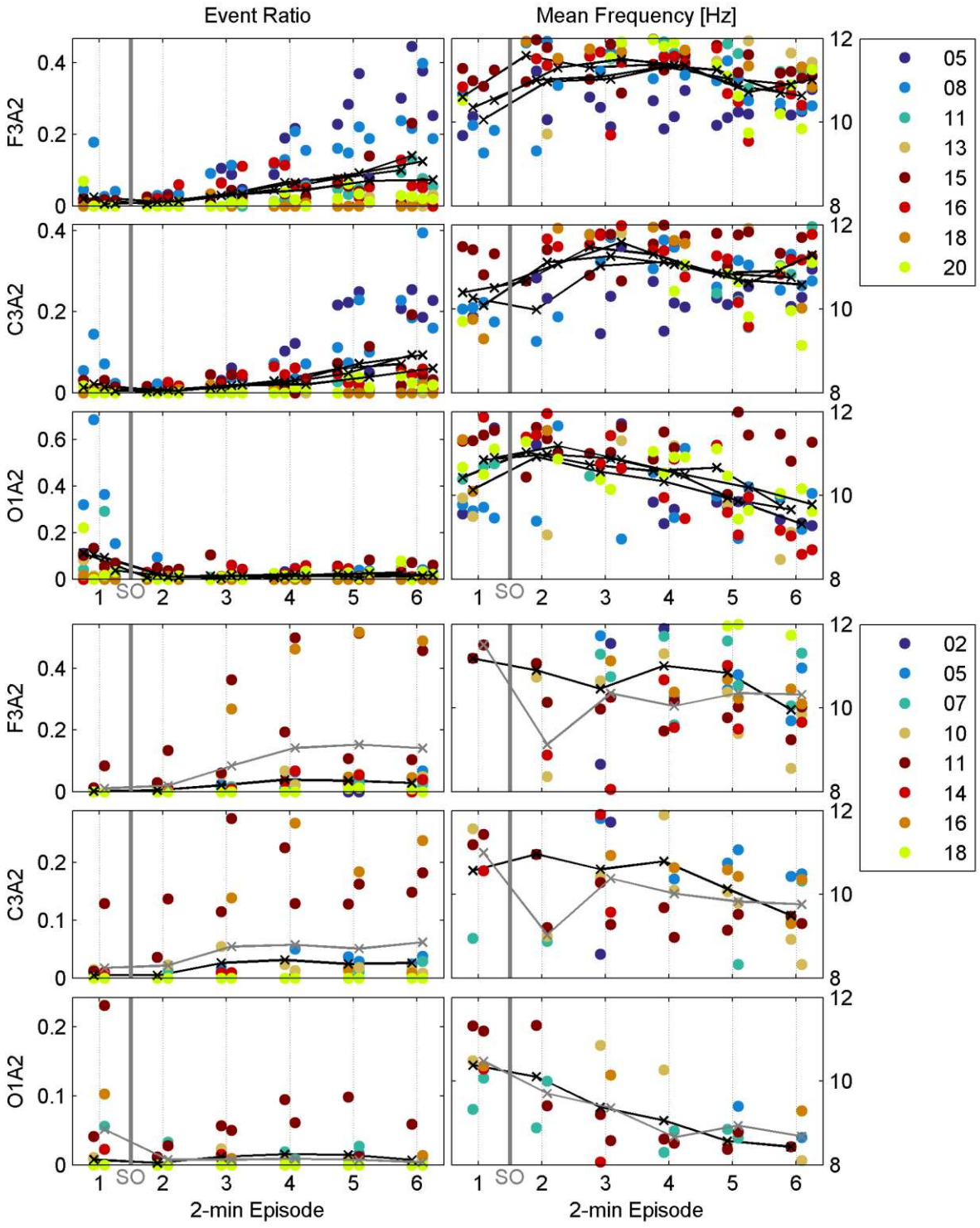

Figure 3: Temporal evolution of oscillatory events in the alpha (8.0-12.0 Hz) band at the SO transition. For details see Figure 2.

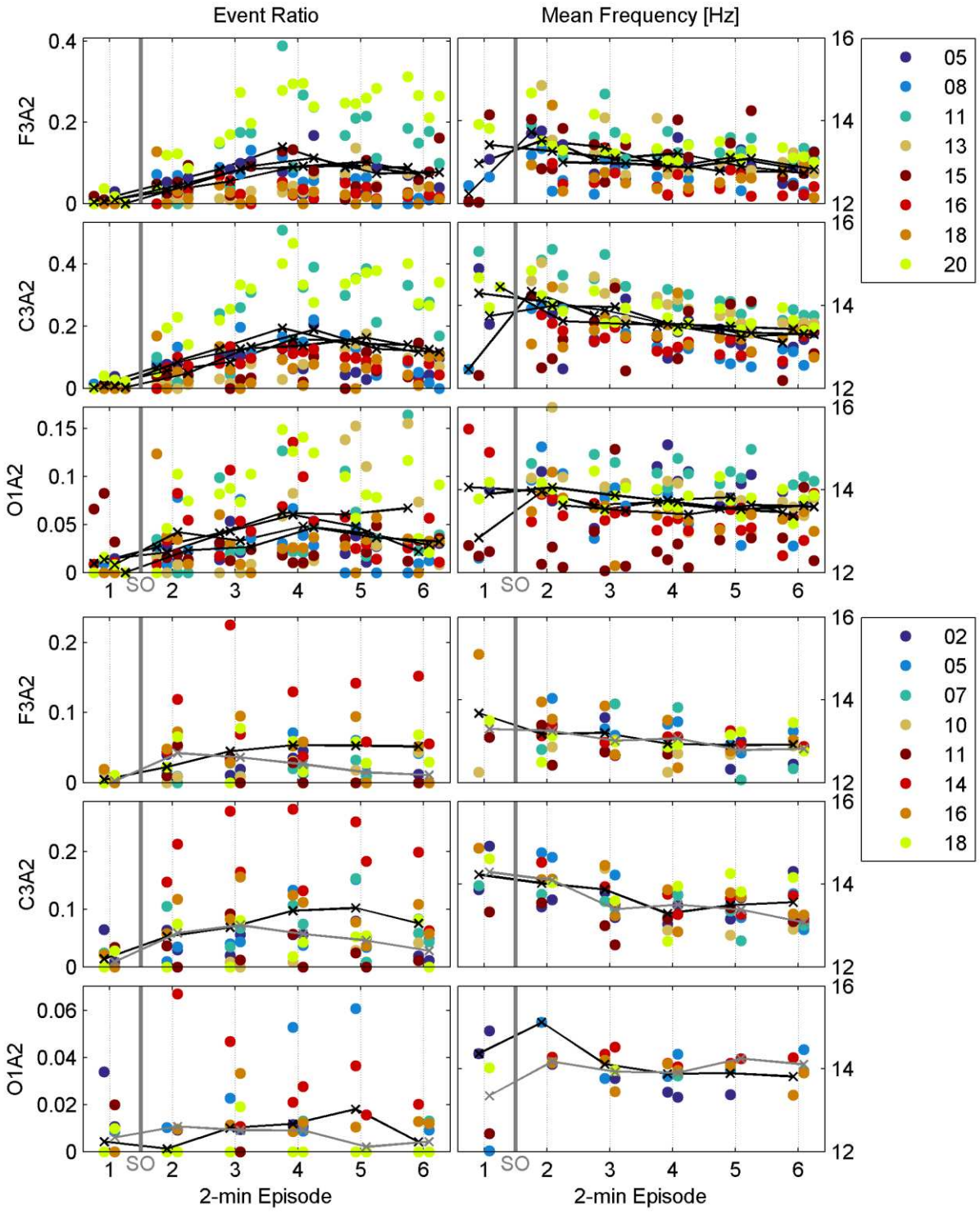

Figure 4: Temporal evolution of oscillatory events in the sigma (12.0-16.0 Hz) band at the SO transition. For details see Figure 2.

Tables

Table 1: Statistical evaluation of the temporal evolution of oscillatory events (event ratio, mean frequency of the events) at the sleep onset transition.

SRD	Response	Derivation					
		F3	C3	O1	F3	C3	O1
delta/theta	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.6325	0.0935	0.6325	0.0487	0.0000	0.0746
	Mean Frequency	Episodes 1-6					
		0.0001	0.0001	0.7932			
alpha	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.3493	0.1426	0.0001	0.0000	0.0000	0.2741
	Mean Frequency	Episodes 1-2			Episodes 2-6		
		0.0044	0.0521	0.0493	0.0665	0.8908	0.0000
sigma	Event Ratio	Episodes 1-4			Episodes 4-6		
		0.0000	0.0000	0.0000	0.0254	0.0652	0.1087
	Mean Frequency				Episodes 2-6		
					0.0000	0.0000	0.0001

MAP Baseline	Response	Derivation					
		F3	C3	O1	F3	C3	O1
delta/theta	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.9721	0.9721	0.5978	0.9721	0.5757	0.4512
	Mean Frequency	Episodes 1-6					
		0.0522	0.0910	0.9747			
alpha	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.6884	0.5339	0.6884	0.1287	0.5284	0.7521
	Mean Frequency	Episodes 1-2			Episodes 2-6		
		0.9177	0.8611	0.8611	0.1927	0.1927	0.1927
sigma	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.1326	0.6000	0.6383	0.3133	0.0650	0.2597
	Mean Frequency				Episodes 2-6		
					0.2402	0.2010	0.2000

MAP Recovery	Response	Derivation					
		F3	C3	O1	F3	C3	O1
delta/theta	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.1863	0.0109	0.0087	0.9721	0.9721	0.9721
	Mean Frequency	Episodes 1-6					
		0.1602	0.1692	0.0359			
alpha	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.6660	0.7408	0.0185	0.0129	0.9761	0.7521
	Mean Frequency	Episodes 1-2			Episodes 2-6		
		0.1927	0.1908	0.3616	0.1927	0.5541	0.2360
sigma	Event Ratio	Episodes 1-2			Episodes 2-6		
		0.0052	0.0042	0.3823	0.0393	0.6722	0.3389
	Mean Frequency				Episodes 2-6		
					0.1367	0.0125	0.8686

Six 2-min episodes (1 to 6; 2 min prior to SO [episode 1], five consecutive 2-min intervals after SO, [episodes 2 to 6]) were analyzed. Three sub-tables partitioning the SRD, MAP baseline and MAP recovery datasets are depicted (grey). Each row corresponds to a particular mixed model of a certain frequency band (delta/theta, alpha or sigma) and one of two responses (event ratio or mean frequency). Shown are the Benjamini-Hochberg adjusted p-values of the post-hoc tests assessing the

temporal evolution (the compared episodes are in grey) of the three derivations (columns). Significant p-values are color coded, with darker tones indicating smaller p-values. An increase in the response with time (e.g. form episode 2 to 6) is indicated in red (estimated parameter has a positive sign), whereas a decrease is blue (estimated parameter has a negative sign).

effect	increase				decrease			
p-value	1-0.05	0.05-0.01	0.01-0.001	0.001-0	0-0.001	0.001-0.01	0.01-0.05	0.05-1
color								

Table 2: Statistical evaluation of the topographical aspects of oscillatory events (event ratio, mean frequency of the events) at the sleep onset transition.

Band	Response	SRD			MAP		
		F3 - C3	C3 - O1	F3 - O1	F3 - C3	C3 - O1	F3 - O1
delta/theta	Event Ratio	0.0000	0.0000	0.0003	0.7733	0.0111	0.0869
	Mean Frequency	0.0385	0.0000	0.0000	0.8248	0.0040	0.0021
alpha	Event Ratio	0.0068	0.4638	0.0002	0.1287	0.2648	0.0063
	Mean Frequency	0.2129	0.0001	0.0000	0.7891	0.1908	0.1419
sigma	Event Ratio	0.0003	0.0000	0.0052	0.0393	0.0000	0.0008
	Mean Frequency	0.0000	0.4420	0.0000	0.0001	0.0417	0.0000

Each row corresponds to a particular mixed model of a certain band (delta/theta, alpha or sigma) and one of the two responses (event ratio or mean frequency). Shown are the Benjamini-Hochberg adjusted p-values of the post-hoc tests assessing topographical overall changes of the SRD and MAP data. Significant p-values are color coded with darker tones indicating smaller p-values. A topographic increase in the response (from frontal to central to occipital; e.g. F3 to C3 or F3 to O1) is indicated in red (estimated parameter has a positive sign), whereas a decrease is blue (estimated parameter has a negative sign).

effect	increase				decrease			
p-value	1-0.05	0.05-0.01	0.01-0.001	0.001-0	0-0.001	0.001-0.01	0.01-0.05	0.05-1
color								

Oscillatory EEG patterns at sleep onset

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Supplemental Material

Spectral analysis and artifact detection

Power density spectra of derivations F3A2, C3A2, and O1A2 were calculated for consecutive 20-s epochs (FFT, detrended, Hanning window, average of five 4-s epochs; matched with sleep stages) resulting in a frequency resolution of 0.25 Hz. Epochs were excluded whenever power in the 20-40 Hz and 0.75-4.5 Hz band exceeded a threshold based on a moving average determined over twenty-one 20-s epochs. The artifact removal procedure concerns spectral analysis, i.e. the average spectra provided in Figures 1, S1 and S2. The detection of oscillatory events is hardly affected by artifacts as they generally do not cause oscillatory activity.

Statistical analyses

Linear mixed models can intuitively model a wide variety of underlying correlation structures by defining different random effects (amongst other advantages like dealing with unbalanced designs and missing values). Mixed models refer to the presence of fixed and random effects. In our analysis the fundamental random effect is due to variability of the subjects assumed to be randomly drawn from the general population. In a nested fashion, we have introduced more random effects to allow for more random variability. In this way we can describe the correlation pattern reasonably well. No random slopes of episode were considered because we have assumed that the subjects follow similar time course and to avoid overfitting.

Table S1 summarizes the models used in 'lmer' from the 'lme4' package of R.

Table S1: *Linear mixed models used to assess the effects of topography (derivation), time (episode) and night (cond).*

Data	Response	Fixed effects	Random effects
SRD	event ratio	derivation*episode	(1|subject) + (1|subject:cond) + (1|subject:cond:derivation) + (1|subject:cond:episode)
	mean frequency	derivation*episode	(1|subject) + (1|subject:cond) + (1|subject:cond:derivation) + (1|subject:cond:episode)
MAP	event ratio	derivation*episode*cond	(1|subject) + (1|subject:derivation) + (1|subject:episode)
	mean frequency	derivation*episode*cond	(1|subject) + (1|subject:derivation) + (1|subject:episode)

Derivation (F3A2, C3A2, O1A2), episode (six 2-min intervals (1 to 6), one before and five consecutive ones after sleep onset), cond (condition: baseline, recovery).

A simpler model, with only subject as a random effect, was also considered, but the AIC of the complex model was always lower compared to the simple one (significant likelihood ratio tests computed with the 'anova' function from the basic 'stats' package of R). Overall the main significance structure did not change markedly, which points to the stability of the results.

As already briefly mentioned in the section statistical analysis, the observed event ratios are values in $[0, 1)$, where it is possible for zero events to occur. But due to a measuring time of 120 s (episode, 2-min interval), we will have a gap from 0 (no events during 120 s) to $1/120$ (one shortest possible event during 120 s) without any data-points. This nature of event ratios always led to structured non-symmetrical residuals. We tried different transformations, including a beta generalized mixed model, but these all failed. Therefore, we used a simple random generation process to substitute the zero values for values from a uniform distribution $Unif(0, 1/120)$. Event ratios were Fisher-z transformed to get an unbounded value $(-\infty, +\infty)$, needed for a linear regression. The Fisher-z transform is defined as $f(x) \coloneqq \tanh^{-1}(2x - 1)$.

To estimate the model coefficients the Restricted Maximum Likelihood (REML) method was used.

For multiple testing we chose to control the False Discovery Rate (FDR) [1] because Family Wise Error Rate (FWER) controlling procedures such as Bonferroni, Holm and Hommel are in general too conservative for non-confirmatory research. The FDR is less conservative, where the most commonly used method is due to [1] (BH method). How to control the FWER and FDR under dependence structure is still an open problem, see for example the informative review of multiple hypothesis testing in [2].

Supplemental references

1. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B-Methodological. 1995; 57 (1): 289-300.

2. Goeman JJ, Solari A. Multiple hypothesis testing in genomics. Statistics in Medicine. 2014; 33 (11): 1946-1978.

Supplemental figures

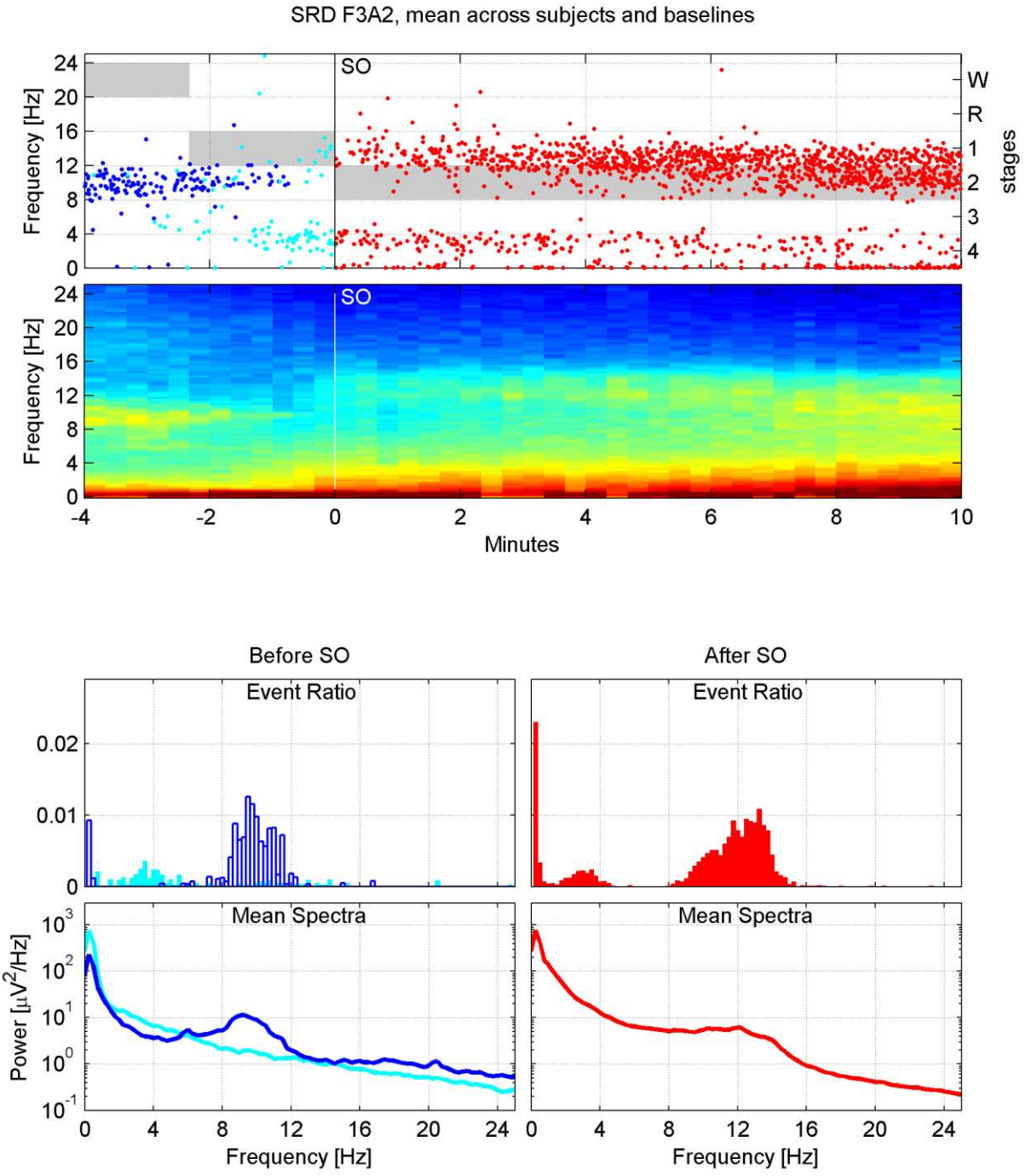

Figure S1: Oscillatory events and spectrograms (derivation F3A2) at the transition into sleep, 4 min prior to and after sleep onset. For details see Figure 1.

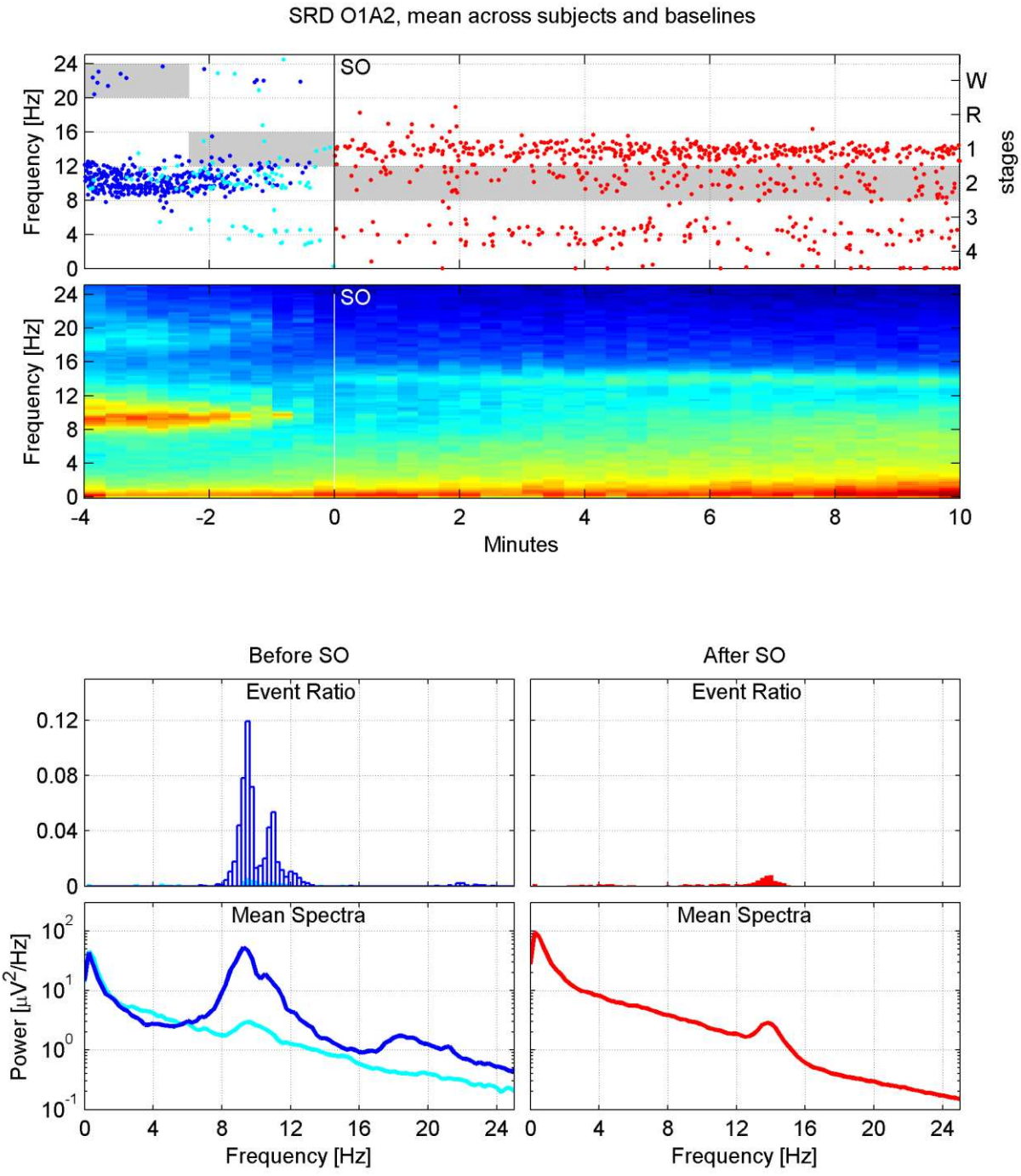

Figure S2: Oscillatory events and spectrograms (derivation O1A2) at the transition into sleep, 4 min prior to and after sleep onset. For details see Figure 1.

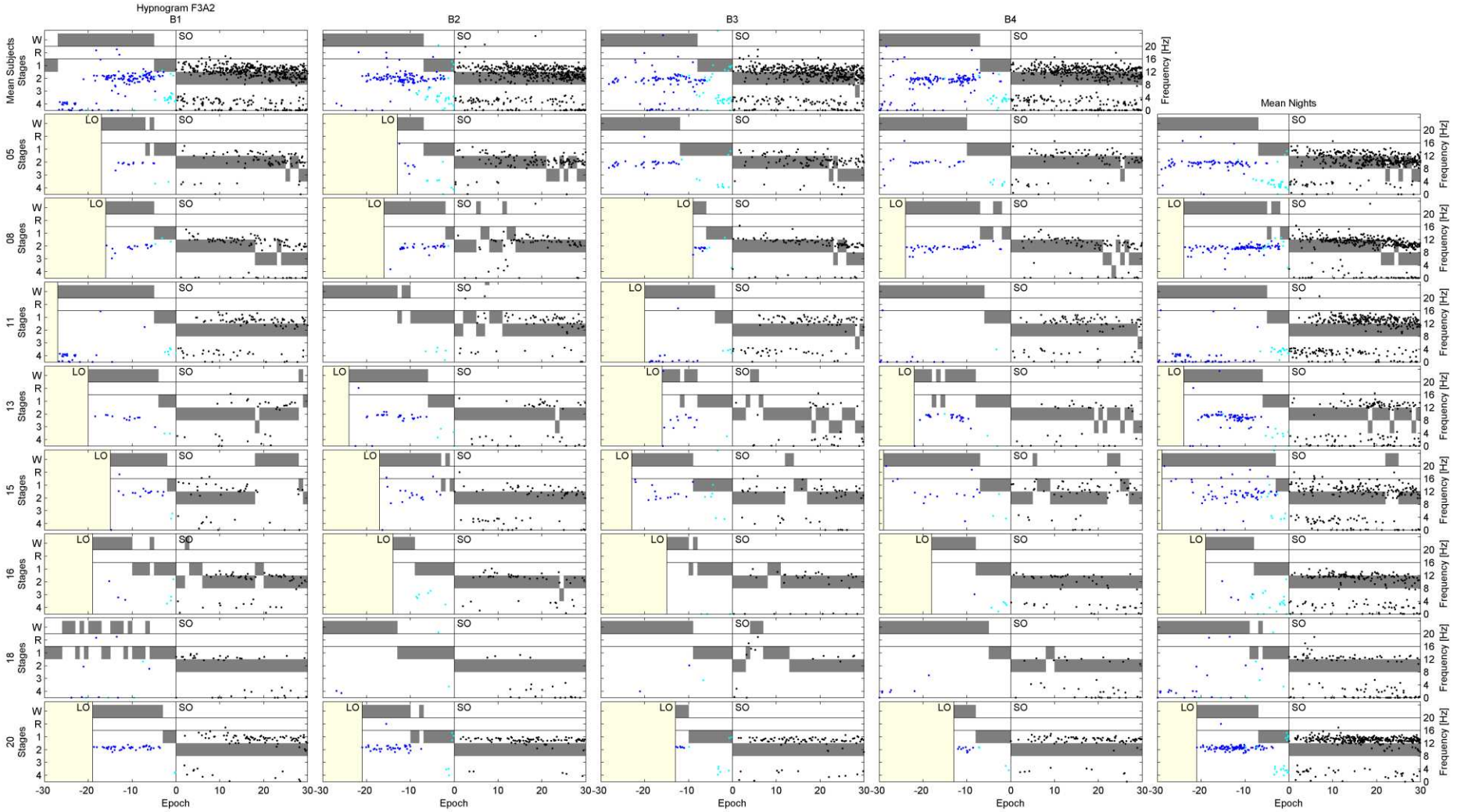

Figure S3: Oscillatory events (derivation F3A2) at the transition into sleep, 10 min prior to and after sleep onset (20-s epochs) of all participants in the SRD study. Sleep onset was defined as the first occurrence of stage 2. Top panels: Occurrence of oscillatory events (frequency axis on right) pooled across the the eight participants superimposed on average sleep stages (axis on left; W: waking, R: REM sleep, 1-4: NREM sleep stages 1-4) of the 4 baseline nights (B1 to B4). Right panels: Occurrence of

oscillatory events pooled across the four baseline nights per participant superimposed on average sleep stages. Dark blue dots: waking; light blue dots: stage 1 (prior to sleep onset); black dots: stage 2 (after sleep onset). Yellow areas time before lights out.

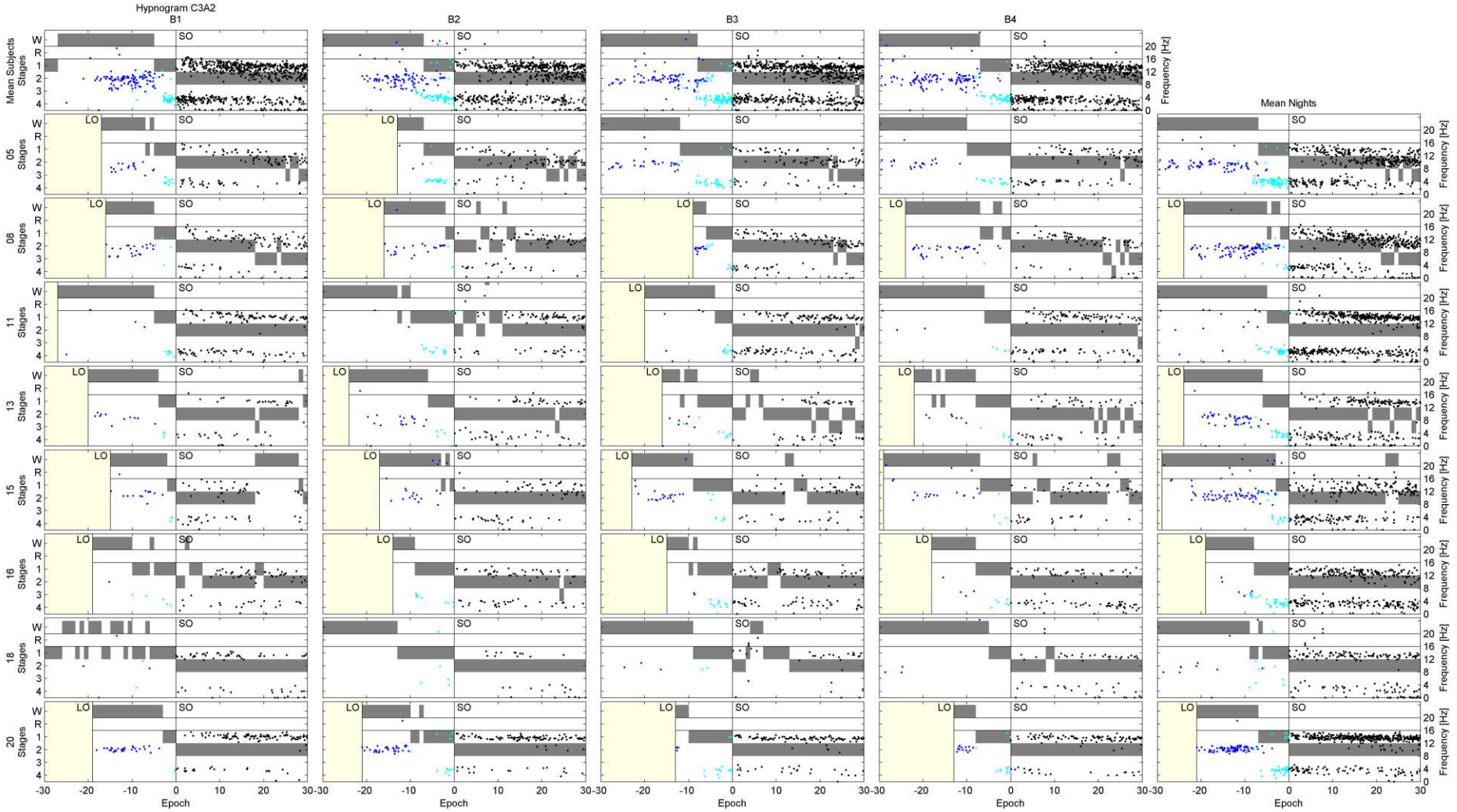

Figure S4: Oscillatory events (derivation C3A2) at the transition into sleep, 10 min prior to and after sleep onset (20-s epochs) of all participants in the SRD study. For details see Figure S3.

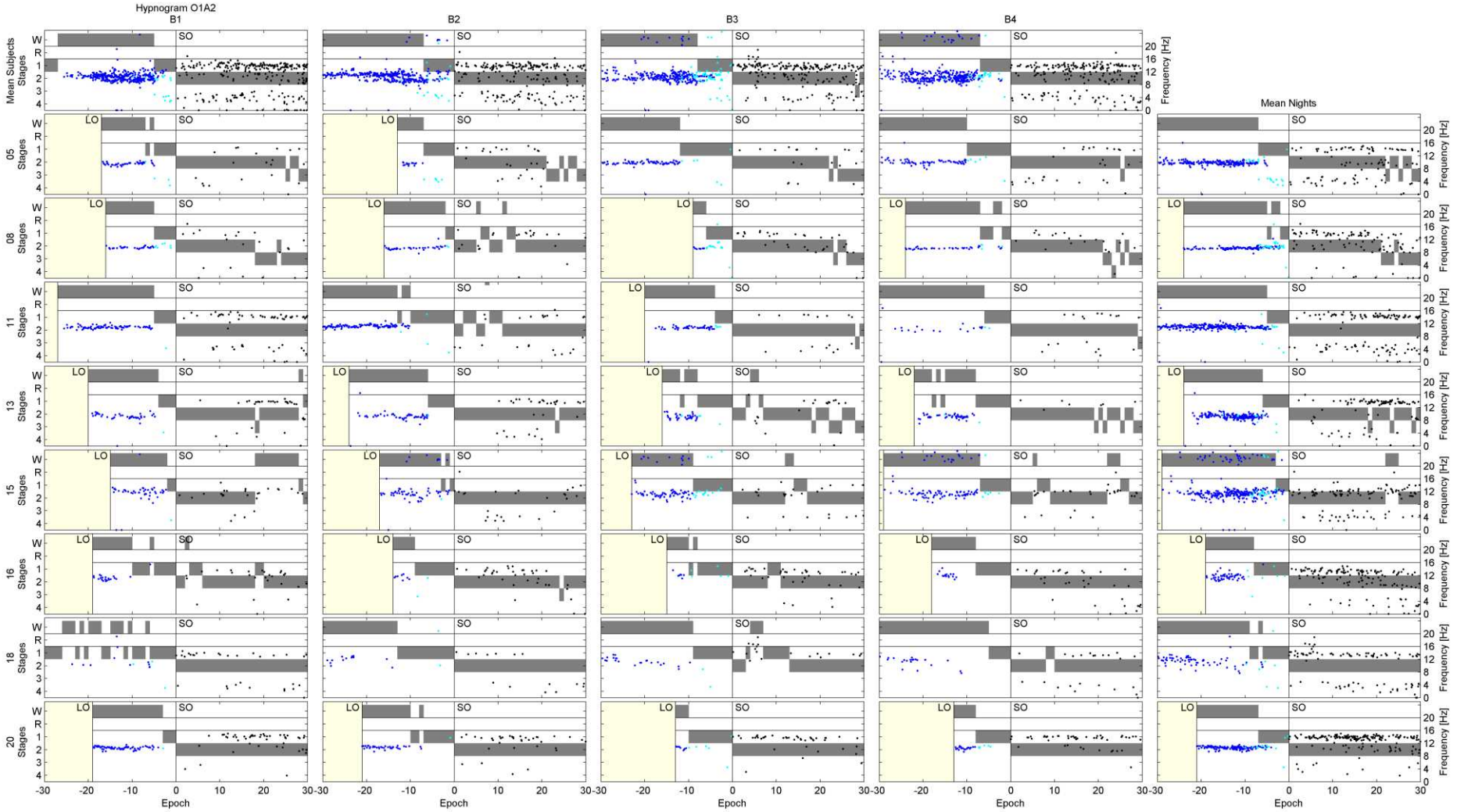

Figure S5: Oscillatory events (derivation O1A2) at the transition into sleep, 10 min prior to and after sleep onset (20-s epochs) of all participants in the SRD study. For details see Figure S3.

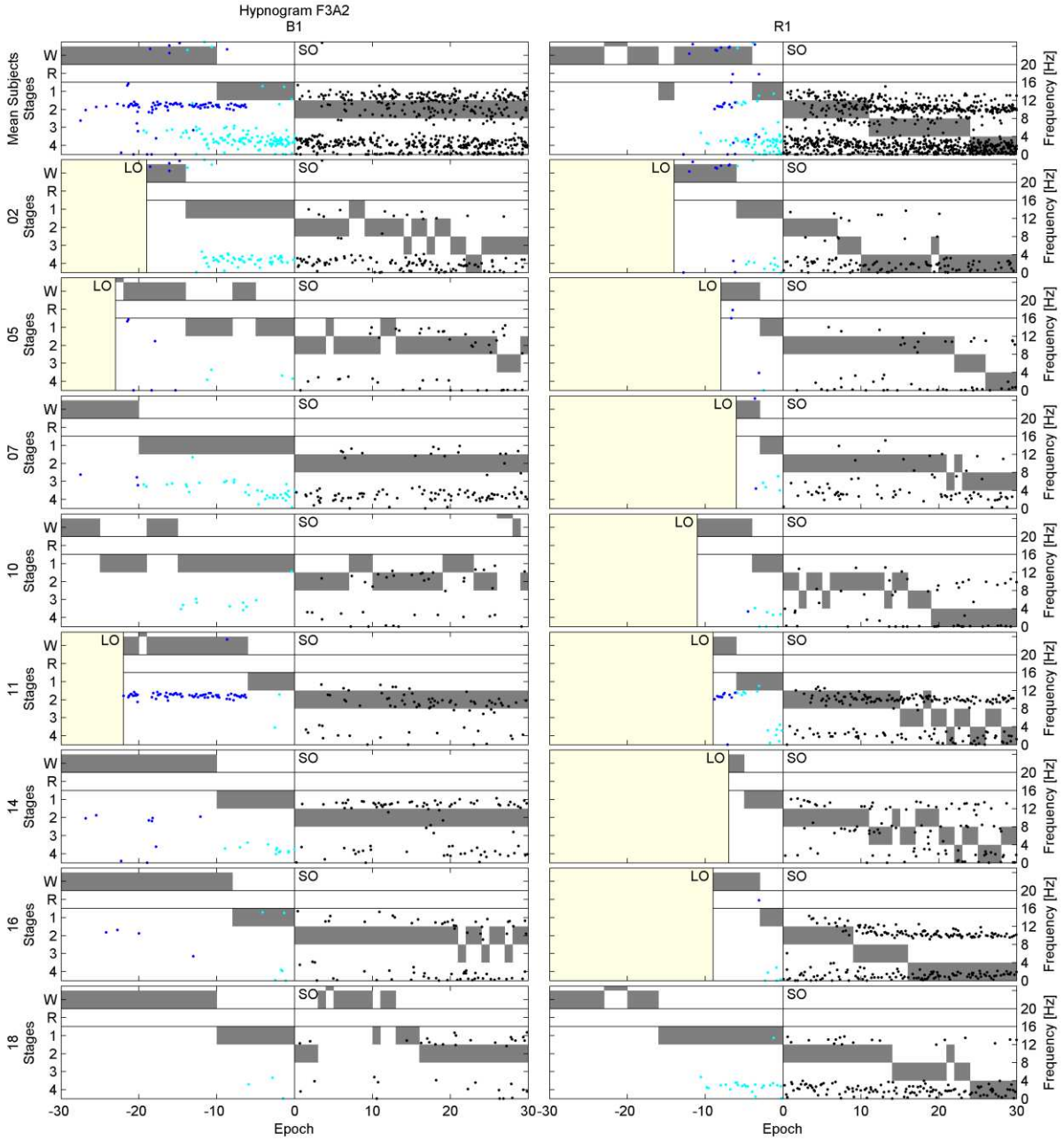

Figure S6: Oscillatory events (derivation F3A2) at the transition into sleep, 10 min prior to and after sleep onset (20-s epochs) of all participants in the MAP study. Sleep onset was defined as the first occurrence of stage 2. Top panels: Occurrence of oscillatory events (frequency axis on right) pooled across the eight participants superimposed on average sleep stages (axis on left; W: waking, R: REM sleep, 1-4: NREM sleep stages 1-4) of baseline (B1) and recovery sleep (R1) after 40 h of sustained wakefulness. Dark blue dots: waking; light blue dots: stage 1 (prior to sleep onset); black dots: stage 2, 3 and 4 (after sleep onset). Yellow areas time before lights out.

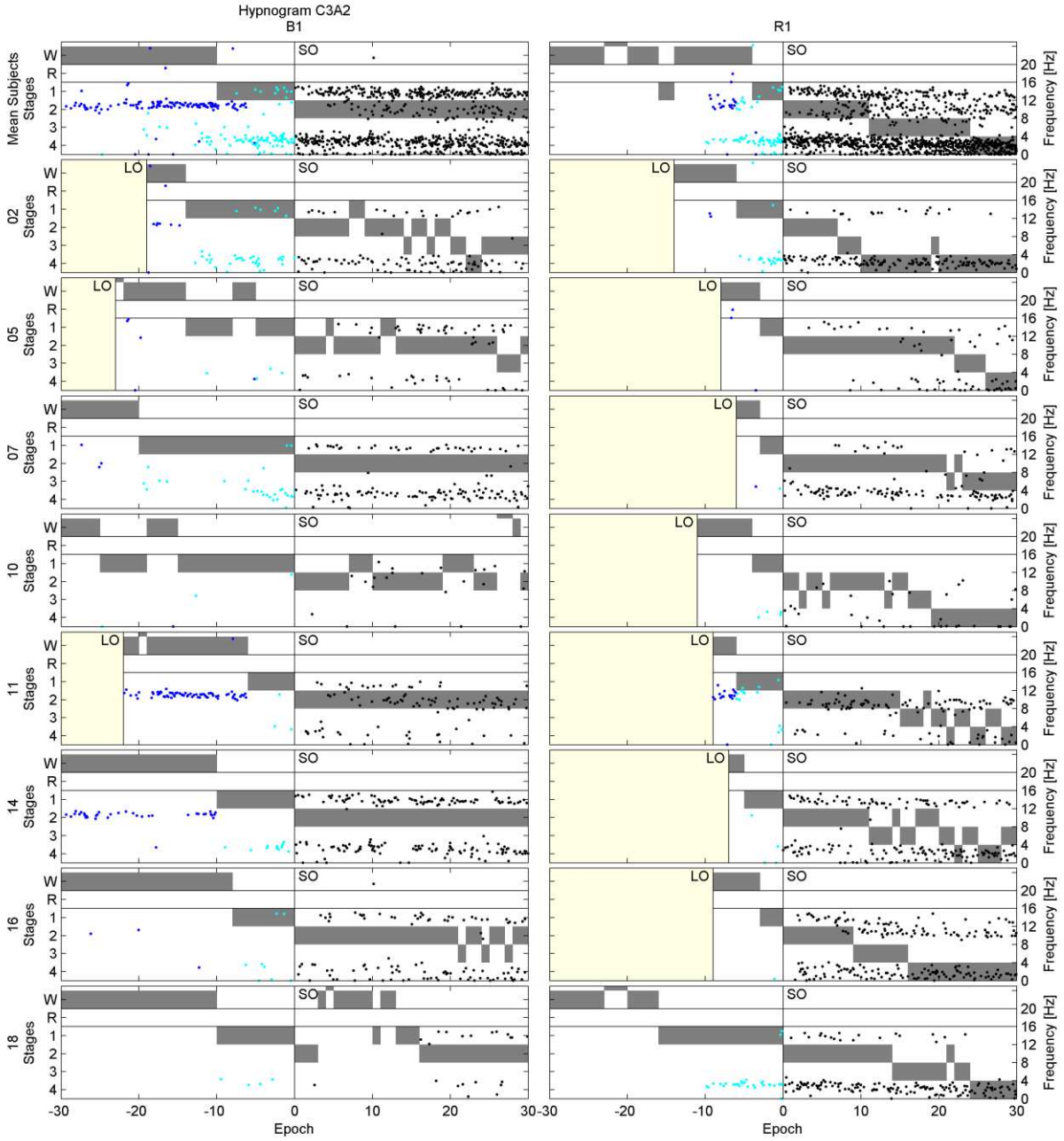

Figure S7: Oscillatory events (derivation C3A2) at the transition into sleep, 10 min prior to and after sleep onset (20-s epochs) of all participants in the MAP study. For details see Figure S6.

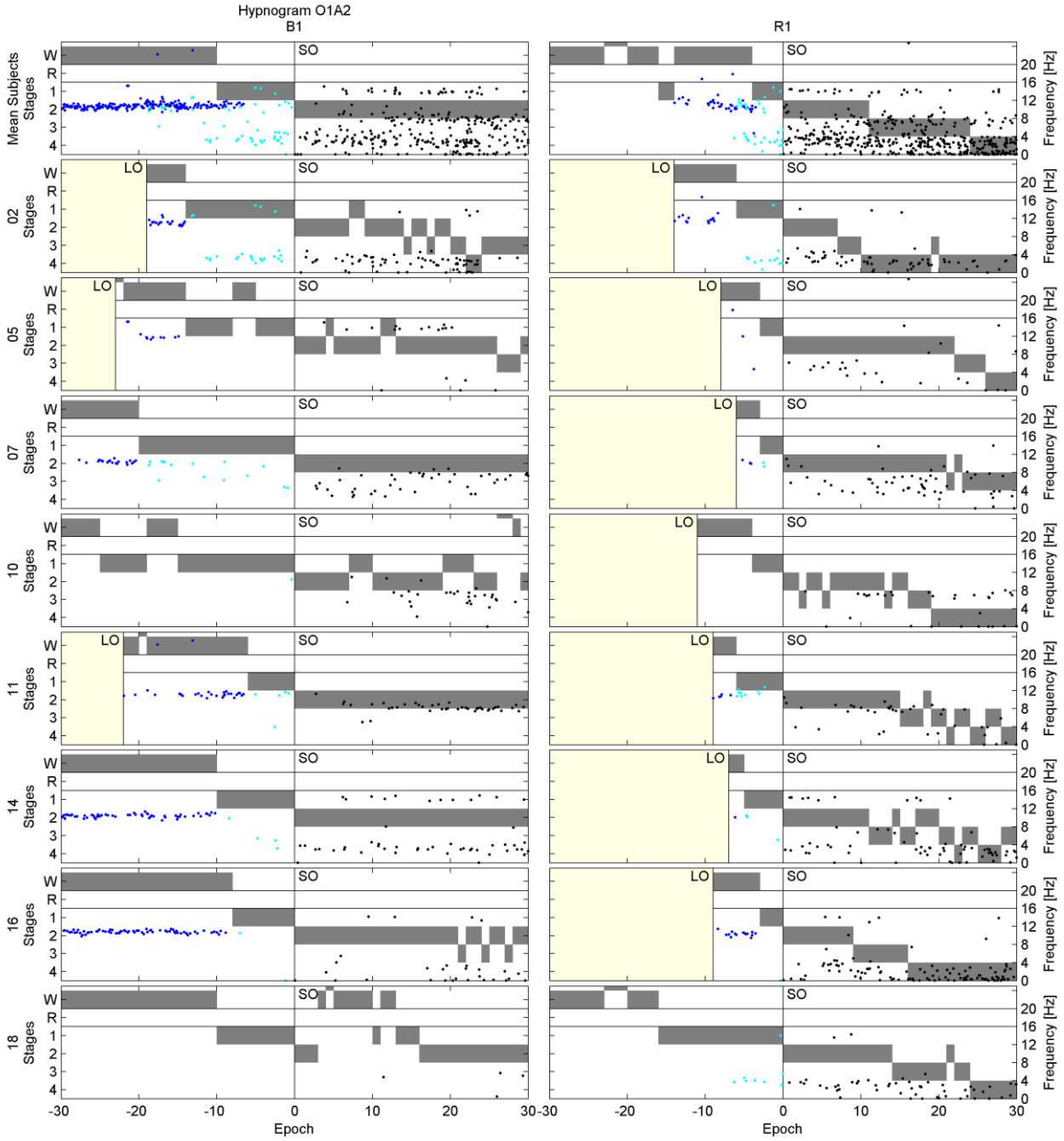

Figure S8: Oscillatory events (derivation O1A2) at the transition into sleep, 10 min prior to and after sleep onset (20-s epochs) of all participants in the MAP study. For details see Figure S6.